Plasma Cortisol Response to Insulin and Circadian Rhythm in Diabetic Subjects

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SUMMARY

The behavior of blood glucose, plasma free fatty acids and cortisol has been studied after insulin administration in subjects with diabetes mellitus without known complications and with normal plasma cortisol circadian rhythm. The mean plasma cortisol response to hypoglycemia in the diabetic subjects was below that of the normal controls, but not statistically significant. The slower rise to normal in the diabetic group was probably due to the lesser degree of hypoglycemia. DIABETES *17*:124-26, March, 1968.

Intravenous administration of insulin in the normal subject is followed by rapid decrease in the blood levels of glucose and plasma free fatty acids (FFA).[1,2] Hypoglycemia stimulates the hypothalamic-pituitary axis with a consequent increase in plasma levels of cortisol,[3] growth hormone,[4,5] epinephrine[6] and norepinephrine.[7] Increased secretion of these hormones serves to restore blood sugar toward normal levels[8] and to elevate plasma FFA.[9-11] The increase in plasma cortisol resulting from the intravenous insulin injection is dependent on the integrity of the hypothalamic-pituitary-adrenal structures.[3,12] Therefore an increase of this hormone after induced hypoglycemia has been used as a test of the function of the hypothalamic-pituitary-adrenal axis.[3,13]

There have been many studies of adrenal function in diabetes mellitus,[14-20] but we are not aware of investigations of the above regulatory pathways. Accordingly, we have examined the levels of blood sugar and plasma FFA and cortisol after intravenous injection of insulin in diabetic patients. In the same persons the circadian rhythm of plasma cortisol has been observed also because its variations may influence the response to hypoglycemic stress,[21] and because alterations in diabetes with vascular complication have been described.[22]

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METHODS

Crystalline insulin (0.1 I.U. per kg. body weight) was given intravenously at 9:00 a.m. to twelve diabetic patients aged twenty-three to seventy years. Ten apparently normal subjects, aged eighteen to fifty-six years, served as controls. The diabetic patients were judged to be under control from treatment with a standard diet (25 calories per kg. of body weight per day) composed of 45 per cent protein, 40 per cent carbohydrate and 15 per cent fat. None had been treated with insulin, and only a few had received tolbutamide. None had detectable vascular complications. After receiving the intravenous insulin, eight of the patients had tachycardia, tremor, perspiration and a decrease in blood sugar of more than 50 mg. per 100 ml. The patients were fasting for over twelve hours prior to testing.

Venous blood samples were obtained before and 15, 30, 45, 60, 90, 120 min. after insulin. Prior to testing, the behavior of plasma cortisol was examined during the day by collecting specimens at 8, 12, 16, and 24 hrs. from diabetic subjects, and subsequently compared with those of fifteen normal subjects.

Plasma cortisol was measured by a fluorimetric method (Tarquini and Toccafondi[23]) in the control sample prior to insulin injection and in the 30, 60, and 120-min. samples after insulin injection. Blood glucose was measured in an AutoAnalyzer according to Hoffman's method.[24] Plasma FFA was measured by the method of Duncombe.[25] The means of the values and the standard deviations of normal and diabetic subjects were computed and statistical comparison of the two groups was made by means of the *t* test.

RESULTS

In eight diabetic patients, the plasma cortisol circadian rhythm was similar to that of fifteen normal controls (figure 1). The mean values of plasma sugar, FFA, and cortisol are given in table 1. There were no significant differences in the fasting concentrations of plasma FFA and cortisol of the diabetic patients and

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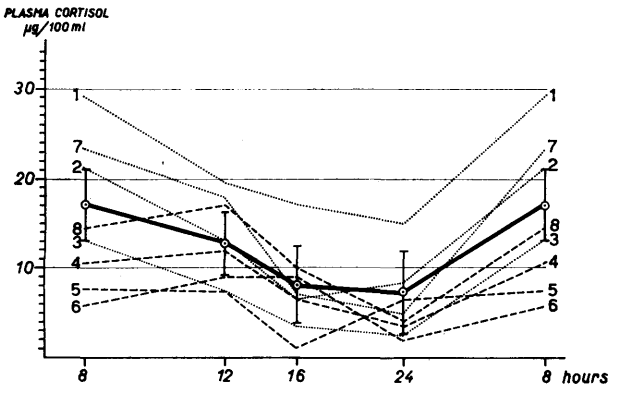

FIG. 1. The plasma cortisol circadian rhythm in diabetic patients. The solid line represents the mean of fifteen normal subjects ± standard deviation.

controls. After intravenous insulin treatment the decrease in blood sugar in ten normal subjects was more rapid and lasting than that observed in the twelve diabetic patients, though the differences were not statistically significant. Indeed, in some diabetic patients the blood sugar did not decline until thirty to forty-five minutes after injection, whereas most of the normal subjects had a fall in sugar by fifteen minutes.

The average plasma cortisol increases under hypoglycemic stress were 7.5 and 14.2 μg./100 ml. in the diabetic and control subjects respectively, but the differences were not statistically significant (table 2). The FFA in normal subjects fell for the first thirty minutes and then rose rapidly, attaining levels higher than at the outset by ninety minutes. In the diabetic patients the decrease in plasma FFA was greater and the concentrations remained lower than the fasting control value even after 120 min. (table 1). The differences were not statistically significant, however.

TABLE 2

The rise in plasma cortisol in each subject after administration of intravenous insulin (0.1 I.U./kg. bw)*

	Diabetic subjects	Normal subjects	P
Plasma cortisol (μg./100 ml.)	7.7±5.6	15.2±7.6	>0.05

*The values represent the mean of eight diabetic and ten normal subjects ± Standard Deviation.

DISCUSSION

In the present study the circadian rhythm of plasma cortisol in uncomplicated diabetes was within normal limits. The average cortisol response to induced hypoglycemia of the patients tested was below the average of the normals, but the difference was not statistically significant. The smaller rise in the diabetic patients may have been related to the smaller degree of hypoglycemia. It has, in fact, been demonstrated that the rise in plasma cortisol in normal man after intravenous administration of insulin is directly proportional to the rate of hypoglycemia.[3,26] The lesser late rise in plasma FFA in the diabetic group may also have been related to the lesser

TABLE 1

The mean plasma sugar, FFA and cortisol in normal subjects and in diabetic patients after administration of intravenous insulin (0.1 I.U./kg. bw)*

Time (minutes)	Plasma sugar (mg./100 ml.) Diabetics	Normals	Plasma FFA (mEq./L.) Diabetics	Normals	Plasma cortisol (μg./100 ml.) Diabetics (8)	Normals (10)
0	107±20	96±7	620±474	421±167	15.2±5.3	13.5±2.6
15	73±29	46±10	502±286	398±61		
30	48±13	43±8	372±99	364±66	14.2±4.5	12.7±8.4
45	60±26	52±9	409±149	421±67		
60	76±26	64±6	465±161	459±72	22.7±4.3	28.7±8.0
90	91±27	81±11	477±167	502±49		
120	97±27	92±13	570±124	512±57	19.9±6.2	20.0±5.8
	Plasma sugar (per cent of fasting level)		Plasma FFA (per cent of fasting level)		Plasma cortisol (per cent of fasting level)	
0	100	100	100	100	100	100
15	66±9	49±16	81±14	82±17		
30	40±8	45±11	60±16	75±14	96±28	87±26
45	54±22	53±9	66±34	88±18		
60	71±21	69±8	75±26	96±16	149±40	189±21
90	85±16	84±2	77±26	107±13		
120	87±19	97±6	92±30	110±12	141±117	147±22

*The values represent the mean of eight diabetic and ten normal subjects ± Standard Deviation.

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degree of hypoglycemia. Thus, insulin-induced hypoglycemia, which has proved useful in the diagnosis of hypothalamico-pituitary-corticoadrenal disorders,[3,13] shows certain limitations in diabetes mellitus, even in carefully selected cases.

The results suggest that in patients with diabetes controlled with diet alone the diencephalo-pituitary-adrenal system functions within normal limits. These observations are in contrast to those of others[27] who obtained responses greater than normal in diabetic subjects when using pyrogens. The patient material of these workers[27] was, however, not homogeneous, as it included subjects that had been treated with insulin. Insulin therapy could lead to adrenal hyperfunction,[17] and account for the different findings.

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